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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,754	02/08/2006	Christopher Frederickson	D6512	6895

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EXAMINER	
SCHLIENTZ, LEAH H	
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1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,754	FREDERICKSON ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *7 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 9-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of the following species in the reply filed on 10/13/2009 is acknowledged: Zn^{2+} as target metal ion, 1,2-bis(2-amino-5-trifluoromethylphenoxy)ethane-N,N,N',N'-tetra acetic acid as complexing agent, and ^{19}F as non-hydrogen imaging nucleus. The traversal is on the grounds that in view of the decisions in *In re Weber* and *In re Haas*, it is improper for the Office to refuse to examine that which Applicants regard as their invention. Applicants consider their invention to comprise a method for in vivo MRI of a target metal ion by administering an MRI contrast agent that comprises a complexing agent that is capable of binding to the target metal ion, acquiring image signals, generating at least one image map using the acquired imaging signal, and correlating intensity of the image pixel with concentration of the target metal ion in the tissue. Applicant asserts that it is this broad technique which is sought to be patented by Applicant, and that the method is not limited to any particular target metal ion, complexing agent or imaging nucleus.

This is not found persuasive. An examination and search burden for patentably distinct species exists due to mutually exclusive characteristics. The species may require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35

U.S.C. 112, first paragraph. In the instant case, while the preliminary prior art search will be drawn to Applicants elected species, if the elected species is not found, the search will be expanded to cover additional non-elected species, per MPEP 803.02. The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 30 recites the limitations "the Zn^{2+}" and "said fluorine." Claim 30 is dependent upon claim 1, however claim 1 does not recite zinc or fluorine. There is insufficient antecedent basis for this limitation in the claim. Appropriate correction is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following reference drawn to non-elected species with regard to chelator and imaging nuclei was found during the search for the elected species upon review of the

International Preliminary Examination Report for PCT/US03/16935, of which the instant application is a national stage entry. It should not be interpreted that a comprehensive search was performed for all non-elected species.

Claims 1-3, 5, 9, 13-16, 20-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Sherry *et al.* (US 5,188,816).

Sherry discloses phosphorous containing macrocyclic chelates which bind certain biological ions with relative specificity. The ^{31}P resonance of these chelators shift to a new position in the NMR spectrum when a metal ion occupies the cavity of the chelate and the NMR chemical shiftof the bound chelate differs for each metal ion. Intracellular concentration of Mg^{2+}, Ca^{2+}, Zn^{2+} may be monitored by ^{31}P NMR (column 1, lines 1-40). The invention also relates to NMR imaging of living subjects, sometimes referred to as magnetic resonance imaging, MRI (column 2, lines 1-22). NMR is an advantageous method for producing cross-sectional images of the human body (column 2, lines 40-42). See column 10 for relative stability of various metal ions and k values. The NMR/MRI scanning disclosed by Sherry would necessitate acquisition, generating and correlating steps in claim 1, as these steps are part of such scanning to provide the image, as related to metal ion concentration, disclosed by Sherry.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 4-6, 9 and 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Song *et al.* (*Am. J. Physiol. Cell Physiol.*, 1995, 269, C318-C322) in view Mason *et al.* (*Magn. Res. Imaging*, 1989, 7(5), p. 475-85 (abstract)).

Song discloses measurement of intracellular calcium concentration in vivo and in situ using ^{19}F-NMR and 5f-BAPTA (page C318, right column). Experiments were performed on rats with surface coil antenna employed for NMR interrogation. The Ca^{2+} indicator, 5F-BAPTA, was infused either intravenously (kidney, spleen) or intraventricularly (brain) as a 100 mg/ml solution of the cell-permeant acetoxy methyl ester (5F-BAPTA-AM) in dimethyl sulfoxide. In all tissues examined, kidney, spleen, and brain $[Ca^{2+}]_i$, was 200 nM (abstract). NMR acquisition parameters are detailed on page C319. See also Figures disclosed page C320 depicting 19F NMR spectra and $[Ca^{2+}]_i$ concentration derived therefrom. Although both kidney and spleen were exposed by surgical incision to place the surface coil in close proximity to the organ and thus maximize signal-to-noise ratio (allowing 5 to 10 min. time resolution), surgical exposure

of organs can be avoided using magnetic resonance imagery-related single volume localization techniques (page C322, left column).

Song does not specifically recite generating an image map comprising intensity of an image pixel derived from said imaging signal acquiring during an imaging scan and correlating the intensity of image pixel on an image map with concentration of metal ion in tissue at said mapping point, or MRI scanning using spin-echo sequence.

Mason discloses multiresonance perfluorocarbon emulsions (Oxypherol and Fluosol-DA) were imaged in tumor-bearing mice using ^{19}F spin-echo magnetic resonance imaging in vivo. Multiple thin-slice fluorine images free of chemical shift artifacts were obtained in 13 minutes and these were correlated with proton images obtained during the same experiment to delineate the anatomic distribution of perfluorocarbons. Sequential images were used to determine the time course of the distribution and the retention of the compounds in tumors and organs. ^{19}F MR spectroscopy was used ex vivo to determine with high sensitivity the relative concentration of perfluorocarbons in different tissues and organs and to confirm the results obtained from imaging experiments. The fluorine images visually demonstrated the preferential localization of the perfluorocarbons in the liver and spleen; shortly after injection, the images also revealed the highly vascularized tumor/chest wall interface. Imaging and spectroscopy together showed that the perfluorocarbons were removed from the blood pool within hours and remained sequestered in tissues at later times; the highest concentrations were found in the spleen and liver, where the agents were retained without spectral changes for the duration of these studies. The

perfluorocarbons accumulated within tumors at dose-dependent concentration, one to two orders of magnitude smaller than those observed in the spleen and liver (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to perform ^{19}F MRI techniques for generating an image map of calcium ion concentration based on the teaching of Song, who teaches in vivo ^{19}F nuclear magnetic resonance spectroscopy for determination of intracellular calcium concentration. One would have been motivated to do so because Song teaches that surgical exposure of organs can be avoided using magnetic resonance imagery-related single volume localization techniques (page C322, left column). One would have had a reasonable expectation of success in doing so because Mason teaches that ^{19}F spin-echo magnetic resonance imaging can be performed in vivo, and can be used to delineate concentration/anatomic distribution of contrast agent in vivo, albeit with a different ^{19}F marker.

Claims 1-6, 9, 13-19, 24, 25, 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Song *et al.* (*Am. J. Physiol. Cell Physiol.*, 1995, 269, C318-C322) in view Mason *et al.* (*Magn. Res. Imaging*, 1989, 7(5), p. 475-85 (abstract)), further in view of Csermely *et al.* (*Biochem. Biophys. Res. Commun.*, 1989, 165(2), p. 838-844 (abstract)).

The rejection over Song in view of Mason is applied as above.

Song teaches determination of calcium concentration rather than zinc, using F-BAPTA. It is for this reason that Csermely is joined.

Csermely discloses that increasing interest is focused on the role of zinc in biological systems. A rapidly growing family of DNA-binding proteins contains "zinc-fingers", where zinc is bound to cysteine or histidine residues. On the other hand zinc is able to displace calcium from its binding sites and in this way it may modify calcium-mediated cellular processes. In the present report dissociation rates of Zn^{2+} and Ca^{2+} complexes with 5-F-BAPTA, a widely used NMR-active calcium indicator, have been measured by two-dimensional ^{19}F NMR exchange spectroscopic methods. The results show that the lifetime of the Zn^{2+} complex is more than five times longer than that of the Ca^{2+} complex. The longer lifetime, when combined with a higher thermodynamical stability of the Zn^{2+} complex, may explain why, in some cellular processes, Zn^{2+} can compete with Ca^{2+} in spite of a presumably high $[Ca^{2+}]/[Zn^{2+}]$ free ion concentration ratio (abstract).

The rejection over Song in view of Mason is applied as above. It would have been further obvious to provide in vivo determination/imaging of zinc concentration, rather than calcium, when the teachings of Song and Mason are taken in view of Csermely. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Csermely teaches that increasing interest is focused on the role of zinc in biological systems, and because it was determined that zinc forms complexes with 5-F-BAPTA having higher kinetic and thermodynamic stability than calcium complexes, as measured by ^{19}F NMR.

Claims 1-6 and 9-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Song *et al.* (*Am. J. Physiol. Cell Physiol.*, 1995, 269, C318-C322) and Mason *et al.* (*Magn. Res. Imaging*, 1989, 7(5), p. 475-85 (abstract)), in view of Csermely *et al.* (*Biochem. Biophys. Res. Commun.*, 1989, 165(2), p. 838-844 (abstract)), further in view of Meade (US 5,707,605) and Woods (US 2002/0114848).

The rejection over Song, Mason and Csermely is applied as above.

Song does not teach diagnosing a disease state wherein the concentration of said metal ion is characteristic of the presence of absence of the disease state.

Meade discloses magnetic resonance imaging agents comprising a paramagnetic metal ion bound to a complex wherein said complex comprises a chelator and a blocking moiety covalently attached to said chelator which binds in at least a first coordination site of said metal ion and which is capable of interacting with a target substance such that the exchange of water in at least said first coordination site is increased (abstract). A blocking moiety may be a calcium binding substance such as known in the art (such as BAPTA), and the target substance may be Ca^{2+}, Mg^{2+}, Zn^{2+}, Na^{+}. The metabolite may be associated with a particular disease or condition within an animal. For example, BAPTA-DOTA derivatives may be used to diagnose Alzheimer's disease or other neurological disorder (column 16, lines 26+; column 20, column 25, lines 45+). Targeting agents are also disclosed.

Woods discloses methods for regulating levels of zinc, cadmium and calcium in humans and for diagnosing, or screening for the risk of developing, diseases associated with abnormal levels of cadmium, zinc and calcium in body fluids and tissues

(title). Diseases associated with unbalanced levels of cadmium and/or unregulated levels of zinc or increased levels of zinc-containing or PGE2-dependent matrix metalloproteinases in body fluids include diabetes, osteoporosis, Alzheimer's disease, hypertension and cancers, such as prostate cancer, colon cancer and breast cancer (paragraphs 0051-0053).

The rejection over Song, Mason, and Csermely is applied as above. It would have been further obvious to diagnose a disease state via ^{19}F MRI imaging of metal ion concentration using F-BAPTA, wherein the concentration of a target metal ion is characteristic of the presence or absence of the disease state, when the teachings of Song, Mason and Csermely are taken in view of Meade and Woods. One would have been motivated to do so because Meade teaches that calcium/zinc can be detected in vivo via MRI using BAPTA chelators, and may be used for imaging Alzheimer's. Since BAPTA chelators have been used to detect ion concentration in vivo (Ca, Zn), and to image Alzheimer's, one of ordinary skill would have had a reasonable expectation of success in imaging Alzheimer's or prostate cancer upon ^{19}F MRI detection of F-BAPTA, since Woods teaches that diseases associated with unbalanced levels of zinc include Alzheimer's and prostate cancer.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-

9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS